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(73) Owner: Laboratorios S.A.L.V.A.T., S.A.
c/ Gallo, 30-36
08950 Esplugues de Llobregat,
Barcelona, Spain

(72) Inventor(s): Manuel Roig Carreras and
Carlos Monserrat Vidal

(74) Agent: Eduardo Maria Espiell Volart

(54) Title: **Self-heating vehicle compositions that can be used in topical treatments**

(57) Summary:

Self-heating vehicle compositions that can be used in topical treatments

Liquid or semisolid vehicle compositions (such as ointments, gels, creams or pastes) which, when applied, generate heat by means of an intimate "in situ" mixing of similar amounts of two constituent parts, an aqueous part (W) consisting mainly of water, and another, organic part (O) consisting mainly of dimethyl sulfoxide, diethylene glycol or polyethylene glycol. As thickening or gelling agents, it contains carbopol, polyvinyl pyrrolidone or glycerol polyacrylate. For self-heating anti-inflammatory compositions, use is made of piroxicam. For self-heating compositions for decongestion of the respiratory passages, eucalyptol, menthol, thymol or guaiacol, or mixtures thereof, are used. For topical application of the compositions use, is made of an impermeable envelope having two tightly isolated compartments, which envelope is cut and allows the simultaneous exit of the two parts of the composition. These compositions have a use in therapy to promote the absorption of the active ingredient without producing the irritation characteristic of rubefacient substances that are sometimes used for this purpose.

NOTE: Examination may be carried out in accordance with Article 37.3.8, Patent Law.

Fig. 1

DESCRIPTION

Self-heating vehicle compositions that can be used in topical treatments

The present invention relates to liquid or semisolid vehicle compositions (such as ointments, gels, creams or pastes) of active pharmaceutical substances for topical application, as well as to a device for application of said compositions.

Prior Art

In the field of cosmetics designed for topical application, certain compositions have been proposed which are self-heating when applied to the body (self-heating compositions). There were basically two chemical mechanisms that have been proposed for generating heat by an "in situ" exothermic reaction between previously separated products.

In the first case, use is made of an oxidation-reduction reaction between two components of the composition, typically between hydrogen peroxide as oxidant and various thiols as reducing agents in patent DE 2,013,994 which relates to cosmetic sprays, and α-oxocarboxylic acids in patent DE 1,944,591 which relates to shaving creams.

In the second case, the heat is produced by an exothermic reaction between one of the components of the composition and the external water which is part of the cosmetic application in question. Thus, for example in patent JP 57064606 (Chem. Abs. 97:28.441 w) relating to hand lotions and shampoos, the heat is obtained by

reaction between the external water and alcohols (ethanol or isopropanol), the latter being the main components (more than 90% of the total composition) of the vehicle compositions of surface-active agents. In patent EP 27,730 relating to similar cosmetic compositions, the predominant components (50-90%) are other alcohols. In all these cases, topical application of the composition requires the use of external water, which is applied simultaneously or is provided by prior wetting.

It is well known that the application of heat increases the speed of absorption and diffusion of many therapeutically active substances that are used topically, thereby increasing the efficacy of these substances. However, none of the aforementioned self-heating compositions proposed in the cosmetic field is of general usefulness in the field of topical therapy. In the first case, this is so because the oxidation-reduction reaction may be intolerable for the patient or chemically incompatible with the active therapeutic ingredient, and, in the second case, because the use of external water is not generally acceptable in the application of a drug, for various possible reasons: lack of aseptic conditions, difficulty of dosage, uncontrolled losses of the drug, etc.

Hence, the task of increasing the effectiveness of topical application of active pharmaceutical substances by local administration of heat is a general problem in therapy. On the other hand, the difference between the temperature of the human body and that of the compositions usually employed in topical treatment causes an unpleasant sensation of cold when these products are applied, a fact which becomes especially problematic in children.

Explanation of the Invention

The present invention provides liquid or semisolid vehicle compositions (such as ointments, gels, creams or pastes) for topical administration of therapeutic active substances in humans or animals, characterized in that, when applied, they generate heat by means of an intimate "in situ" mixing of similar amounts of two previously separated liquid or semisolid component parts, namely an aqueous part (W) and another, organic part (O), said aqueous part consisting mainly of water, for example in the form of an aqueous gel, and the organic part consisting mainly of organic products which, being liquid or semisolid *per se* or present in thickened form or as a gel and being pharmaceutically acceptable for topical use, and being fully or substantially miscible with water and give an exothermic reaction upon mixing, and the principal pharmaceutical active substances are suspended or dissolved in one of the two parts or in both, and the aforementioned parts may contain minor amounts of nontherapeutic components such as thickeners, stabilizers, antioxidants, perfumes, etc.

The organic products that are most suitable for being the main components of the organic parts (O) are dimethyl sulfoxide, diethylene glycol or polyethylene glycol. Especially suitable as thickening or gelling agents are carbopol (up to 5% in one or both parts), polyvinylpyrrolidone (up to 5%), glycerol polyacrylate (up to 30%) and hydroxyethylcellulose (up to 10%).

It is of advantage if the aqueous part contains an amount of a water-soluble and pharmaceutically acceptable base that is sufficient to obtain a substantially neutral pH.

Suitable pharmaceutical active substance to be administered by means of the self-heating compositions of the invention include a nonsteroidal anti-inflammatory agent such as piroxicam, cinoxicam, tenoxicam or diclofenac; a local anesthetic such as benzyl alcohol, lidocaine or benzocaine; an antibiotic such as ciprofloxacin or amoxicillin; an expectorant or antiseptic agent such as eucalyptol, thymol, guaiacol, menthol or camphor; an anticellulitic agent such as xanthines or buttercup [Ranunculus] extract, and an antihistamine such as promethazine.

Particularly preferred for anti-inflammatory self-heating compositions is the active substance piroxicam. For self-heating decongestants of the respiratory passages, the following active substances are preferred: eucalyptol, menthol, thymol or guaiacol, or a mixture thereof.

For topical application of the liquid or semisolid self-heating compositions and vehicles of active therapeutic substances of the present invention, any type of known two-compartment devices can be used, such as envelopes, sprays or two-compartment syringes. However, in view of its ease of preparation, it is recommendable to use a device of the type shown in Fig. 1, a device which is also a subject of the present invention and which comprises an envelope that is impermeable in its interior, is refillable and closable, and is of the type used for the individual dosage of liquid or semisolid formulations in cosmetics, but having two tightly isolated compartments, one for containing the aqueous part (W) and the other for containing the organic part (O) which are separated by a sealed zone which makes it possible that before application, the envelope be folded along a line (a) which traverses it, allowing the opening of the

envelope by means of a cut (with scissors, by hand with the aid of grooves or a part cut) along a line of cutting, e.g., (b), (b') or (b") intersecting the fold line (a), obtaining with said cut two adjacent openings which permit the simultaneous exit of the two parts of the self-heating composition, (W) and (O). It is advantageous if the dosages provide similar quantities of the two parts. An advantage of this device is that its preparation and filling easily adapt to existing machinery for packing cosmetic gels into envelopes that have been made impermeable.

The advantages of using the self-heating compositions of the present invention are due to the generation of heat, as a result of which temperatures of up to approximately 45°C are attained. Mention may also be made of the following advantages, among others:

a) Promoting the absorption of the active substance due to local vasodilatation produced by the heat;

b) Not causing the irritation characteristic of the rubefacient substances that are sometimes used for this purpose;

c) Providing a pleasant sensation of heat, avoiding the thermal contrast with the skin temperature, which is especially important in the case of children.

The following examples show two particular types of composition which are found especially adequate.

Examples

Example 1

Self-heating anti-inflammatory composition

Aqueous part (W): 1.0 g of benzyl alcohol and 0.14 g of diisopropylamine are dissolved in 100 mL of distilled water. 0.20 g of carbopol is added and the mixture is stirred until a transparent gel is formed.

Organic part (O): 1.0 g of piroxicam and 1.8 g of carbopol are dissolved in 100 mL of dimethyl sulfoxide, and the mixture is stirred until a transparent gel is formed.

Self-heating test: At a room temperature of 24-26°C, 40 g of each of the aqueous part (W) and organic part (O) of the above composition are homogeneously mixed and the temperature is measured at specific intervals after mixing. The results are shown in Table 1.

TABLE 1

Self-Heating Test

Time, minutes	Temperature, °C
0	44
0.66	43
1.66	42
3	41
5	38.5
10	37
15	36
30	33

Example 2

Self-heating composition for decongestion of respiratory passages

Aqueous part (W): 15 g of glycerol polyacrylate and 0.60 g of 96% ethanol are dissolved in 100 mL of distilled water, and the mixture is stirred until a transparent gel is formed.

Organic part (O): 2.5 g of menthol, 1.20 g of eucalyptol, 0.25 g of thymol and 0.45 g of guaiacol are dissolved in 70 g of polyethylene glycol 600. To the resulting solution is added 25.6 g of glycerol polyacrylate and the mixture is stirred until a transparent gel is formed.

Example 3

Dosage, packing and application of the self-heating compositions

In an envelope sealed in its center as shown in Fig. 1 were placed 5 g of aqueous part and 5 g of organic part of the compositions of Example 1 and 2 in the respective tightly isolated compartments. After folding the envelope along the seal line (a), the envelope was cut along line (b), the lower part was pressed in order to pour the two parts simultaneously on the skin, the skin was gently rubbed by hand and a pleasant heat sensation was produced, the gels being rapidly absorbed.

CLAIMS

1. Liquid or semisolid vehicle compositions (such as ointments, gels, creams or pastes) for topical administration of therapeutic active substances in humans or animals, **characterized** in that when applied, they generate heat by means of an intimate "in situ" mixing of similar amounts of two previously separated liquid or semisolid component parts, one of them an aqueous part and the other an organic part, said aqueous part consisting mainly of water, for example in the form of aqueous gel; and said organic part consisting mainly of organic products which, being liquid or semisolid *per se* or present in thickened form or as a gel and being pharmaceutically acceptable for topical use, are fully or substantially miscible with water and give an exothermic reaction upon mixing, the principal pharmaceutical active substances being suspended or dissolved in one of the two parts or in both; and the aforementioned parts possibly containing lesser amounts of nontherapeutic components such as thickeners, stabilizers, antioxidants, perfumes, etc.

2. Compositions according to Claim 1, **characterized** in that the organic products which constitute the main portion of the organic part are dimethyl sulfoxide, diethylene glycol or polyethylene glycol.

3. Compositions according to Claim 2, **characterized** in that the organic product which constitutes the main portion of the organic part is dimethyl sulfoxide.

4. Compositions according to Claim 2, **characterized** in that the organic product which constitutes the main portion of the organic part is diethylene glycol.

5. Compositions according to Claim 2, **characterized** in that the organic product which constitutes the main portion of the organic part is polyethylene glycol.

6. Compositions according to any of Claims 1 through 5, **characterized** in that one or both parts contain up to 5% carbopol as thickening or gelling agent.

7. Compositions according to any of Claims 1 through 5, **characterized** in that one or both parts contain up to 5% polyvinylpyrrolidone as thickening or gelling agent.

8. Compositions according to any of Claims 1 through 5, **characterized** in that the aqueous part contains up to 10% hydroxyethylcellulose as thickening or gelling agent.

9. Compositions according to any of Claims 1 through 5, **characterized** in that one or both parts contain up to 30% glycerol polyacrylate as thickening or gelling agent.

10. Compositions according to any of the preceding claims, **characterized** in that the aqueous part contains an amount of a water-soluble and pharmaceutically acceptable base that is sufficient to obtain a substantially neutral pH.

11. Compositions according to any of the preceding claims, **characterized** in that the pharmaceutical active substance is a nonsteroidal anti-inflammatory agent such as piroxicam, cinoxicam, tenoxicam or diclofenac; a local anesthetic such as benzyl alcohol, lidocaine or benzocaine; an antibiotic such as ciprofloxacin or amoxicillin; an expectorant or antiseptic agent, such as eucalyptol, thymol, guaiacol,

menthol or camphor; an anticellulitic agent such as xanthines or buttercup [Ranunculus] extract; or an antihistamine such as promethazine.

12. Compositions according to any of the preceding claims, **characterized** in that the pharmaceutical active substance is piroxicam.

13. Compositions according to any of the preceding claims 1 through 11, **characterized** in that the pharmaceutical active substances are eucalyptol, menthol, thymol or guaiacol, or a mixture thereof.

14. Two-compartment device (e.g., of the envelope, spray or syringe type) for topical application of a liquid or semisolid compositions, **characterized** in that the composition applied in self-heating and is a vehicle for therapeutic active substances, as indicated in Claim 1.

15 Two-compartment device according to Claim 14, **characterized** in that it comprises an envelope that is impermeable in its interior, is refillable and closable, and is of the type used for the individual dosage of liquid or semisolid formulations in cosmetics, but having two tightly isolated compartments, one for containing the aqueous part (W) and the other for containing the organic part (O), which are separated by a sealed zone which makes it possible that before application, the envelope be folded along a line (a) which traverses it; allowing the opening of the envelope by means of a cut (with scissors, by hand with the aid of grooves or a part cut) along a line of cutting, e.g., (b), (b') or (b") intersecting the fold line (a), obtaining with said cut two adjacent openings which permit the simultaneous exit of the two parts of the self-heating composition, (W) and (O).

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RELEVANT DOCUMENTS

Category	Documents cited	Claims involved
X	GB 1,042,529-A (AMERICAN HOME PRODUCTS CORPORATION) Sept. 14, 1966 * Pages 1-4, Examples 9, 11, 12 *	1-3, 5, 6, 13
Y		1, 2, 4-12, 14
Y	ES 8500738-A (PFIZER CORPORATION) Nov. 1, 1984 * Pages 1, 6, 7, 11, 12; Examples 2, 3, 8, 9, 10 *	1, 2, 4-12
Y	US 3,723,324-A (V.J. PIERCE) March 27, 1973 * Column 1 *	14
A	EP 0,027,730-A (JOHNSON COMPANY, LIMITED) Apr. 29, 1981	1, 2, 4, 5
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A	US 3,592,936-A (A.D. MARCUS) July 13, 1971	1-3, 6
A	US 4,781,926-A (HYON et al.) Nov. 1, 1988 * Column 3, Examples *	1-8
A	GB 1,357,000-A (BRITISH-AMERICAN TOBACCO CO. LTD) June 19, 1974 * Pages 1-3 *	1, 2, 4, 5

Category of documents cited

X	Of particular relevance	O	Refers to unwritten disclosure
Y	Of particular relevance in combination with other/s of the same category	P	Published between the priority date and filing date of the application
A	Reflects the prior art	E	Prior document, but published after the filing date of the application

The present report was drawn up ⊠ for all claims.

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Examiner: Asha Sukhwani

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